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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,674	11/15/2001	Richard J. Whitley	27373/33716	8665

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,674	WHITLEY ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 29 June 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-32 are pending and under examination in the instant application. An action on the merits follows.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (c) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7-8, 12-21, 24-26, 31 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130. Please note that the Andreansky et al. reference lists several authors who are not listed as inventors of the instant invention. Therefore this reference qualifies as prior art under 35 U.S.C.102(a).

The applicant claims a herpes simplex virus type 1 genome comprising two copies of a cDNA encoding IL-4, each operatively linked to an EGR-1 promoter and an HBV polyadenylation signal, wherein the IL-4 encoding cDNAs have replaced the viral $\gamma_1$34.5

genes in the viral genome. The applicant further claims wherein the IL-4 encoding cDNAs have replaced the Bst EII-StuI fragment of the $\gamma_1$34.5 genes. In addition, the applicant claims pharmaceutical compositions comprising said recombinant HSV and methods of treating neoplastic disease of the CNS comprising administering said recombinant HSV to a target tumor.

Andreansky et al. teaches a recombinant HSV-1 virus which comprises $\gamma_1$34.5 genes in which the Bst EII-StuI fragment of the $\gamma_1$34.5 genes have been replaced by either IL-4 or IL-10 cDNAs operatively linked to EGR-1 promoters and HBV polyA sequences (Andreansky et al., page 122, in particular Figure 1). Andreansky et al. further teaches formulating the recombinant HSV encoding IL-4 for *in vivo* use and directly administering the virus to target tumors in the brain resulting in inhibition of tumor growth (Andreansky et al., page 125, Figure 7). Thus, by teaching all the elements of the claims as written, Andreansky et al. anticipates the instant invention as claimed.

Claims 1-4, 14, 19-21, 24 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al. The applicant claims a recombinant herpes simplex virus which lacks all or part of both $\gamma_1$34.5 genes and which comprises an expressible cytokine-encoding DNA. The applicant further claims said recombinant HSV wherein the cytokine is IL-4, IL-2, gamma interferon, or TNF alpha. The applicant also claims pharmaceutical compositions comprising said recombinant HSV and methods of treating neoplastic disease of the CNS comprising administering said recombinant HSV to a target tumor.

Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches the G207 virus which is an HSV virus in which both copies of the $\gamma_1$34.5 genes contain a 1 kb deletion of the Bst EII-StuI fragment present in the $\gamma_1$34.5 genes (Rabkin et al., column 5, lines 28-41). Rabkin et al. also teaches that the immunomodulator is a cytokine, particularly cytokines such as IL-2, IL-4, gamma interferon and TNF-alpha (Rabkin et al., column 7, lines 50-67, and column 8, lines 27-37). Rabkin et al. further teaches formulating the mutant HSV as pharmaceutical compositions and administering the compositions directly to tumors *in vivo* (Rabkin et al., columns 2-3 and 7). Thus, by teaching all the elements of the claims as written, Rabkin et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were

made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 6, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al. in view of U.S. Patent No. 5,328,688 (7/12/94), hereafter referred to as Roizman '688. The applicant claims recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible cytokine-encoding DNA wherein the $\gamma_1$34.5 genes have a stop codon at a Bst EII site in said genes. Regarding claims 22 and 23, these claims have been rejected under 35 U.S.C. 112, second paragraph below, because it is unclear whether they are directed to the recombinant HSV product or a method of using the product. However, in either case, claims 22 and 23 would be rendered obvious by the combination of Rabkin and Roizman '688 and so have been included in the instant rejection.

Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches that the immunomodulator is a cytokine, particularly cytokines such as IL-2, IL-4, gamma interferon and TNF-alpha (Rabkin et al., column 7, lines 50-67, and column 8, lines 27-37).

Rabkin et al. differs from the instant invention by not particularly teaching that the HSV virus which is incapable of expressing functional $\gamma_1$34.5 gene products has a stop codon at the Bst EII site in the $\gamma_1$34.5 gene. Roizman '688 supplements Rabkin et al. by teaching several different methods for making recombinant HSV which are incapable of expressing a functional $\gamma_1$34.5 gene product. Roizman '688 teaches that the $\gamma_1$34.5 gene can be inactivated by deleting a portion of the coding sequence of the $\gamma_1$34.5 genes or by introducing a stop codon at a BstEII site in the $\gamma_1$34.5 gene (Roizman '688, column 2). Specifically, Roizman '688 teaches HSV R4009 in which a stop codon has been introduced at a BstEII site in both copies of the $\gamma_1$34.5 genes (Roizman '688, column 2, lines 19-23). Roizman et al. further teaches that such viruses are rendered avirulent by the inactivation of the $\gamma_1$34.5 genes (Roizman et al., column 20, claim 4). Thus, based on the motivation to make and use mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator to treat tumors of the CNS as taught by Rabkin et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to modify any of the $\gamma_1$34.5 inactivated HSV taught by Roizman '688 such as HSV R4009 in which a stop codon has been introduced at a BstEII site in both copies of the $\gamma_1$34.5 genes to include an expressible nucleotide sequence encoding at least one immunomodulator. Based on the detailed instructions provided by Roizman '688 for making HSV R4009, and the instructions in Rabkin et al. for inserting expressible nucleotide sequences encoding a cytokine into mutant HSV, the skilled artisan would have had a reasonable expectation of success in making and using a recombinant HSV

which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible cytokine-encoding DNA, wherein the $\gamma_1$34.5 genes have a stop codon at a Bst EII site in said genes.

Claims 1, 9-11, 19, and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130 **or** U.S. Patent No. 6,379,674 B1 (4/30/02), hereafter referred to as Rabkin et al., in view of U.S. Patent No. 5,641,651 (6/24/97), hereafter referred to as Roizman '651. The applicant claims recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible cytokine-encoding DNA, wherein the cytokine-encoding DNA is under the promoter-regulatory control of a synthetic HSV-derived promoter comprising promoter sequences upstream of the transcription initiation site of the α4 gene operatively linked to the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene. The applicant further claims methods of treating neoplastic disease of the CNS comprising administering said recombinant HSV to a target tumor.

Both Andreansky et al. **or** Rabkin et al. teach recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible cytokine-encoding DNA. Specifically, Andreansky et al. teaches a recombinant HSV-1 virus which comprises $\gamma_1$34.5 genes in which the Bst EII-StuI fragment of the $\gamma_1$34.5 genes have been replaced by either IL-4 or IL-10 cDNAs operatively linked to EGR-1 promoters and HBV polyA sequences (Andreansky et al., page 122, in particular Figure 1). Andreansky et al. further teaches formulating the recombinant HSV encoding IL-4 for *in vivo* use and directly

administering the virus to target tumors in the brain resulting in inhibition of tumor growth (Andreansky et al., page 125, Figure 7). Alternatively, Rabkin et al. teaches mutated HSV viruses which are incapable of expressing a functional $\gamma_1$34.5 gene product and which comprise at least one expressible nucleotide sequence encoding at least one immunomodulator (Rabkin et al., column 3, lines 8-15). In particular, Rabkin et al. teaches the G207 virus which is an HSV virus in which both copies of the $\gamma_1$34.5 genes contain a 1 kb deletion of the Bst EII-StuI fragment present in the $\gamma_1$34.5 genes (Rabkin et al., column 5, lines 28-41). Rabkin et al. also teaches that the immunomodulator is a cytokine, particularly cytokines such as IL-2, IL-4, gamma interferon and TNF-alpha (Rabkin et al., column 7, lines 50-67, and column 8, lines 27-37). Rabkin et al. further teaches formulating the mutant HSV as pharmaceutical compositions and administering the compositions directly to tumors *in vivo* (Rabkin et al., columns 2-3 and 7).

Neither of Andreansky et al. nor alternatively Rabkin et al. teach using a synthetic HSV promoter to drive cytokine expression. Roizman '651 supplements Andreansky et al. or Rabkin et al. by teaching a synthetic HSV-derived promoter comprising promoter sequences upstream of the transcription initiation site of the α4 gene operatively linked to the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene, and the use of said promoter to drive transcription of genes in recombinant HSV (Roizman '651, column 2, and columns 11-12). Roizman '651 further provides motivation for using a synthetic HSV-derived promoter to express foreign proteins using recombinant HSV by teaching that the synthetic promoter expresses gene products throughout the infectious process of the virus and overproduces the gene product

(Roizman '651, column 2, lines 16-20, and column 3, lines 7-14). Thus, based on the motivation to use the synthetic HSV promoter provided by Roizman '651, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the synthetic promoter described by Roizman '651 to drive expression of the cytokine genes in the recombinant HSV taught by Andreansky **or** alternatively Rabkin et al. Further, based on the substantial direction provided by all of Andreansky et al., Rabkin et al., and Roizman '651 for making and modifying recombinant HSV, and the high level of skill in the art of molecular and viral biology at the time filing, the skilled artisan would have had a reasonable expectation of success in making and using recombinant HSV which lack all or part of both $\gamma_1$34.5 genes and which comprise an expressible cytokine-encoding DNA, wherein the cytokine-encoding DNA is under the promoter-regulatory control of a synthetic HSV-derived promoter comprising promoter sequences upstream of the transcription initiation site of the α4 gene operatively linked to the transcription initiation site and the 5' transcribed non-coding sequence of the γ_1U_L19 gene.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating neoplastic disease of the central nervous system comprising administering to a target tumor a recombinant herpes simplex virus incapable of expressing an active $\gamma_1$34.5 gene product and comprising an expressible DNA encoding IL-4, does not reasonably provide enablement for said methods wherein the recombinant HSV encodes a cytokine other than IL-4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The broadest claims, as exemplified by claim 19, read on treating neoplastic disease of the CNS by administering recombinant HSV incapable of expressing an active $\gamma_1$34.5 gene product and comprising an expressible DNA encoding any cytokine. Claims 21 and 23 recite a markush group of cytokines which consist of IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, gamma interferon, and tumor necrosis factor alpha.

While the specification broadly states that any cytokine and most particularly those listed in claims 21 and 23 can be expressed from the recombinant HSV of the instant invention and used to treat tumors, the specification fails to provide an enabling disclosure for treating tumors of the CNS using recombinant HSV which encode any cytokine other than IL-4. The specification's working examples provide direct evidence that recombinant HSV encoding IL-10, one of the preferred cytokines recited in the claims, is incapable of treating a tumor of the CNS. In example 5, the specification compares intratumoral injection of HSV encoding IL-4 with HSV encoding IL-10 for the treatment of an established glioma. Figure 6 shows that while treatment with HSV

encoding IL-4 statistically increased survival, treatment with HSV encoding IL-10 did not. The specification does not provide any additional evidence that any cytokine other than IL-4 would be capable of treating a tumor of the CNS when expressed by a recombinant HSV incapable of expressing an active $\gamma_1$34.5 gene product.

Further, prior art published at the time of filing also demonstrates the failure of recombinant HSV incapable of expressing an active $\gamma_1$34.5 gene product and comprising an expressible DNA encoding IL-10 in treating gliomas in the brain (see Andreansky et al. (1998) Gene Therapy, Vol. 5, 121-130). Andreansky et al. also teaches that while some cytokines have been shown to have anti-tumor activity *in vivo*, other cytokines have not. Specifically, Andreansky et al. teaches that IL-5, IL-10, and TGF-β2 fail to generate anti-tumor immune responses, lack localized tumor killing, and/or inhibit tumor immunogenicity (Andreansky et al., page 122, paragraph 1). Thus, Andreansky et al. and the working examples presented in the instant specification provide clear evidence that cytokines differ substantially in their ability to generate anti-tumor immune responses and mediate tumor killing, and that IL-10, IL-5, and TGF-β2 do not possess anti-tumor activity. Most particularly, Andreansky et al. and the instant specification clearly demonstrate that recombinant HSV incapable of expressing an active $\gamma_1$34.5 gene product and comprising an expressible DNA encoding IL-10 is incapable of treating tumors of the CNS. Therefore, based on the bread of the claims, the nature of cytokines and the documented differences in their activity and ability to induce anti-tumor immunity and/or tumor killing, and the evidence of record that cytokines such as IL-10,

IL-5, and TGF-β2 do not possess anti-tumor activity, it would have required undue experimentation for the skilled artisan to practice the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20 and 22 recite " The method of claim 16...". Claims 21 and 23 depend on claims 20 and 22 respectively. Claim 16 is a product claim not a method claim and recites, " The recombinant virus of claim 14..". Thus, claims 20-23 are confusing in that it is unclear whether the applicant intends to further limit the product of claim 16 or whether the applicant actually intends to further limit the method of claim **19.** If the applicant in fact wishes to claim the product and not the method, then claims 21 and 23 are further improper dependent claims in that claim 16 is already limited to an HSV which encodes IL-4. Thus, the metes and bounds of the claims as written cannot be determined.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not

available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER